PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Luc R. Mongeon, Jesus Casas-Bejar, H. Toby Markowitz, Daisy P. Cross, Janelle Blum, Michael Ebert and Timothy G. Laske	Confirmation No.	2842
Serial No.:	10/663,570	Group Art Unit:	3762
Filed:	September 15, 2003	Customer No.:	28863
Examiner:	Michael William Kahelin		
Docket No.:	1023-203US01		
Title:	DELIVERING GENETIC MATERIAL TO A STIMULATION SITE		

CERTIFICATE UNDER 37 CFR 1.8 I hereby certify that this correspondence is being transmitted via the United States Patent and Trademark Office electronic filing system on October 26, 2010.

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REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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Sir:

This Reply Brief is responsive to the Examiner's Answer dated September 1, 2010. The period of response for filing this Reply Brief runs through November 1, 2010.

No fees are believed to be due at this time. Please charge any additional fees that may be required or credit any overpayment to Deposit Account No. 50-1778.

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STATUS OF CLAIMS

Claims 21–24, 26, 29–33, 35–42, and 46–54 are pending and are the subject of this appeal. Claims 21–24, 26, 29–33, 35–42, and 46–54 are set forth in Appendix A of the Appeal Brief filed on June 18, 2010. Originally filed claims 5–8 were canceled in an Amendment filed on August 4, 2006. In addition, originally filed claims 11 and 27 were canceled in an Amendment filed on June 28, 2007, and originally filed claims 20, 25, 28, and 34 were canceled in an Amendment filed on October 29, 2007. Claims 40–45 were added by way of an Amendment filed on August 4, 2006. Claim 46 was added by way of an Amendment filed on November 7, 2008. Claims 1–4, 9, 10, 12–19, and 43–45 were canceled in an Amendment filed on November 7, 2008 as being drawn to a nonelected invention. Claims 47–54 were added by way of an Amendment filed on October 20, 2009

Claims 21–24, 26, 29–33, 35–42, and 46–54 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Soykan et al. (U.S. Patent No. 6,151,525, hereinafter "Soykan") in view of Heil, Jr. et al. (U.S. Patent No. 4,819,662, hereinafter "Heil") and Girouard et al. (U.S. Patent Application Publication No. 2004/0158289, hereinafter "Girouard").

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

Appellant submits the following ground of rejection to be reviewed on appeal: the rejection of claims 21–24, 26, 29–33, 35–42, and 46–54 under 35 U.S.C. § 103(a) as allegedly being obvious over Soykan in view of Heil and Girouard.

ARGUMENT

In the Examiner's Answer to Appellant's Appeal Brief, the Examiner provided a clarification of the rejection of the claims. For brevity, this Reply Brief only addresses aspects of these new arguments. Accordingly, this Reply Brief is not intended to address all arguments provided in the Examiner's Answer, and Appellant requests full consideration of all arguments set forth in the Appeal Brief filed on June 18, 2010. Appellant respectfully requests separate review of each set of claims argued under separate headings in the Appeal Brief.

CLAIMS 21–24, 26, AND 29–33

Soykan in view of Heil, and further in view of Girouard lacks any teaching that would have suggested a medical lead that includes a porous electrode, a genetic material that causes expression of at least one of a connexin or a gap-junction by tissue at the stimulation site, where the expression of the at least one of the connexin or the gap-junction by the tissue at the stimulation site increases the conductivity of the tissue, and a chamber body that defines a chamber containing a polymeric matrix that absorbs the genetic material and degrades to elute the genetic material to tissue at the stimulation site via the porous electrode, as recited by independent claim 21.

In support of the rejection of independent claim 21 as being obvious over Soykan in view of Heil and Girouard, the Examiner stated that Soykan discloses a lead that delivers electrical stimulation to a tissue site and elutes genetic material from a polymeric matrix.[1] The Examiner acknowledged that Soykan does not disclose or suggest required elements of Appellant's claimed lead, such as a chamber that elutes material from a porous electrode or a genetic material that is adapted to cause expression of at least one of connexin or a gap junction.[2] The Examiner looked to both Heil and Girouard in an attempt to cure the identified deficiencies in the Soykan reference. In particular, the Examiner asserted that Heil discloses "a lead with a removable

[1] Office Action dated February 19, 2010 at p. 2, item 4.
[2] *Id.* at p. 3, item 4.

chamber that elutes substances through a porous electrode" and Girouard discloses "providing a cardiac therapy comprising delivering connexin."[3]

In the Examiner's Answer, the Examiner asserted that although Soykan discloses that a genetic material may be incorporated into a carrier, which may be an electrical stimulation device, Soykan is silent as to precisely where on or in the electrical stimulation device the carrier resides.[4] Therefore, the Examiner reasoned, "looking to prior art carrier configurations, such as Heil's, would require only ordinary skill in the art."[5] The Examiner attempted to reason that "an artisan of ordinary skill would be motivated to make this modification to provide the agent *at the site of electrical therapy*."[6] As discussed in further detail below, one having ordinary skill in the art would not have looked to Heil to modify Soykan in order to "provide the agent *at the site of electrical therapy*"[7] because Soykan already discloses providing a genetic material at the site of electrical therapy.

As discussed in the Appeal Brief, Soykan discloses that genetic material may be coated on or otherwise incorporated into a carrier, such as an electrical stimulator capsule or a catheter a catheter advanced to the desired site for treatment.[8] In a technique disclosed by Soykan, a damaged myocardium is repopulated with undifferentiated contractile cells, e.g., via a genetic material, and the newly formed tissue is augmented with electrical stimulation to cause the newly formed tissue to contract in synchrony with the heart.[9] In the Examiner's Answer, the Examiner acknowledged that, in Soykan, "the cells that are the target of the therapeutic agent are the same cells that are the target of the electrical therapy."[10] For at least these reasons, Soykan indicates that the coating or catheter provides genetic material at the site of electrical stimulation delivery. Accordingly, one having ordinary skill in the art would not have looked to Heil to modify

[3] *Id.*
[4] Examiner's Answer at p. 8.
[5] *Id.*
[6] *Id.* (emphasis in original; some emphasis omitted).
[7] *Id.* (emphasis in original; some emphasis omitted).
[8] Soykan at col. 11, ll. 2–7 and col. 12, ll. 33–40 and 60–66; *see* Appeal Brief filed June 18, 2010 at pages 8 and 9.
[9] Soykan at col. 4, ll. 37–42.
[10] Examiner's Answer dated September 1, 2010 at p. 9.

Soykan for the reason proposed by the Examiner, and the Examiner has failed to establish a *prima facie* case of obviousness.

Absent access to Appellant's disclosure, one having ordinary skill in the art would not have looked to modify Soykan in view of Heil for the reason proposed by the Examiner because Soykan discloses that genetic material can be coated on or otherwise incorporated into a carrier, such as an electrical stimulation device, and that the tissue formed by delivery of the genetic material is stimulated by the electrical stimulation device, thereby indicating the genetic material disclosed by Soykan is already provided at the site of electrical therapy. The art does not provide any basis for asserting that the genetic agent needs to be applied "at the electrode" in order to "provide the agent at the site of electrical therapy,"[11] as asserted by the Examiner, or that the coating disclosed by Soykan is incapable of providing the genetic agent "at the site of electrical therapy."[12]

Moreover, even if it would have been desirable to modify Soykan in view of Heil to "apply the agent at the electrode,"[13] there is no apparent reason why the specific configuration disclosed by Heil would have been used. Indeed, incorporating the coating disclosed by Soykan into a recess in a crimp tube of a lead disclosed by Heil would not necessarily be required to apply a genetic agent at the electrode. The Examiner has not established that the coating disclosed by Soykan would be incapable of applying "the agent at the electrode."[14] Therefore, the Examiner's proposed reason for modifying Soykan to place the genetic material in a recess defined by the crimp tube disclosed by Heil is insufficient to support a *prima facie* case of obviousness.

In an alternative basis for supporting the assertion of obviousness, the Examiner asserted that "modifying Soykan's genetic material-eluting cardiac device with Heil's known prior art drug-eluting cardiac device is a simple substitution of one known element for another to obtain

[11] *Id.* at p. 8 (emphasis omitted).
[12] *Id.* (emphasis omitted).
[13] *Id.* at p. 9.
[14] *Id.*

the predictable results of controlled release of a therapeutic agent."[15] As noted in the Appeal Brief, even in the case of a claim rejection based on the "predictable results" rationale, identification of a reason why a person of ordinary skill would have combined the elements in the manner proposed by the Examiner is important.[16] The Examiner has failed to identify a rational reason why a person of ordinary skill would have combined the Soykan system and the Heil electrode. Therefore, the Examiner failed to establish a *prima facie* case of obviousness with respect to independent claim 21.

In the Examiner's Answer, the Examiner addressed Appellant's remarks made in the Appeal Brief by stating that "there is simply nothing in the record to indicate any actual difference between drug and genetic material warranting 'secondary considerations' of nonobviousness."[17] This reflects a misunderstanding of Appellant's remarks. Appellant's remarks were directed at emphasizing that the modification of the Soykan system to include the porous electrode and recess (for retaining a matrix including a therapeutic drug) disclosed by Heil is not merely a simple substitution of one known element for another, nor does the modification proposed by the Examiner necessarily provide a "predictable result" of "controlled release of a therapeutic agent," as asserted by the Examiner.[18]

A drug, as disclosed by Heil, and a genetic material, as disclosed by Soykan, may have different purposes and different properties, which is a factor working against the "simple substitution" rationale relied on by the Examiner. As a result of the differences between a drug and a genetic material, there may be different considerations and objectives for elution of a drug versus elution of a genetic material. As an example of the differences between a drug and a genetic material, Appellant has recognized that expression of at least one of connexin or a gap-junction may provide advantages over elution of a drug, such as a desired effect that lasts longer and is more localized than that of drug.[19] Thus, contrary to the Examiner's assertions,

[15] Final Office Action dated January 23, 2009 at p. 6, item 12 (Response to Arguments section) and Examiner's Answer dated September 1, 2010 at p. 9.
[16] MPEP 2143, *citing KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).
[17] Examiner's Answer dated September 1, 2010 at p. 9.
[18] Final Office Action dated January 23, 2009 at p. 6, item 12 (Response to Arguments section).
[19] Appellant's originally filed disclosure at p. 2, ll. 6–13.

substituting a genetic material for the drug disclosed by Heil would not have been obvious because it is not a simple substitution nor does the modification proposed by the Examiner necessarily provide a "predictable result" of "controlled release of a therapeutic agent," as asserted by the Examiner.[20]

As discussed in the Appeal Brief, it would not have been obvious to modify Soykan in view of Heil, and further in view of Girouard. Furthermore, Soykan was modified in view of Heil, and further in view of Girouard, the resulting lead would not have included a genetic material that causes expression of at least one of a connexin or a gap-junction by the tissue at the stimulation site, wherein the expression of the at least one of the connexin or the gap-junction by the tissue at the stimulation site increases the conductivity of the tissue, as recited by Appellant's claim 21.

Girouard does not provide any indication that connexin is advantageous over the genetic material disclosed by Soykan, or provides some expected beneficial result over the coating disclosed by Soykan. Thus, it is unclear why one having ordinary skill in the art would have looked to modify the genetic material disclosed by Soykan to include connexin.

Moreover, contrary to the Examiner's assertions, modifying Soykan in view of Girouard is not merely "a simple substitution of one known element for another to obtain the predictable results of repairing damaged heart tissue."[21] Girouard proposes the use of a genetic material for a different purpose than Soykan. The Examiner asserted that modifying Soykan in view of a genetic material disclosed by Girouard involves a simple substitution because both Soykan and Girouard disclose the use of a "cardiac-repairing genetic material." However, Soykan is not merely directed at repairing damaged heart tissue. Instead, Soykan discloses the use of genetic material to convert noncontracting cells to contracting cells in an infarct zone of a patient's myocardium, i.e., *in vivo*.[22] On the other hand, Girouard discloses a transgene that encodes, e.g., connexin-40, connexin-42, and connexin-43, to condition donor cells *in vitro*, prior to

[20] Final Office Action dated January 23, 2009 at p. 6, item 12 (Response to Arguments section).
[21] *Id.* at p. 6, item 13 (Response to Arguments section).
[22] Soykan at col. 7, ll. 54–60.

administration of the donor cells into a region of injured tissue of the patient.[23] In particular, Girouard uses the genetic material to subject donor cells to exogenous agents, such as differentiation factors, growth factors, and the like.[24] The donor cells are conditioned outside of the patient, and then subsequently introduced into the tissue region to be treated. Thus, while Girouard discloses providing cell therapy of living tissue, Girouard is only directed to the use of exogenous cells,[25] which may be conditioned using genetic material. The use of genetic material to condition exogenous cells by Girouard is contrary to Soykan, which discloses the conversion of cells in an infarct zone within the patient using genetic material.

In the Examiner's Answer, the Examiner asserted that Girouard "recognizes that the vectors may be applied either *in vitro* or *in vivo*, and does not require an *in vitro* conditioning step,"[26] and cited paragraph [0044] and FIGS. 1A and 1C to support this assertion. The Examiner is mischaracterizing the Girouard disclosure. Girouard does not disclose that all genetic material disclosed by Girouard is configured to be applied *in vitro* and *in vivo*. Paragraph [0044] of Girouard is merely part of a definition section, in which Girouard generally defines a "vector" or "construct" as referring to a macromolecule or a complex of molecules comprising a polynucleotide to be delivered to a host cell either *in vitro* or *in vivo*.[27] It is improper for the Examiner to rely on this definition to assert that all genetic material disclosed by Girouard is configured to be applied *in vitro* and *in vivo*.

Appellant's independent claim 21 recites a genetic material that causes expression of at least one of a connexin or a gap-junction by the tissue at the stimulation site. With respect to the transgene that encodes connexin-42 or connexin-43, Girouard discloses that the transgene is used to biologically condition donor cells by subjecting the donor cells to exogenous agents, such as transgenes.[28] Girouard only discloses subjecting donor cells to exogenous agents, such as

[23] Girouard at ¶¶ [0076], [0129], and [0146].
[24] *Id.* at ¶ [0146].
[25] *Id.* at Abstract.
[26] Examiner's Answer dated September 1, 2010 at page 10 (emphasis omitted).
[27] Girouard at ¶ [0044].
[28] *Id.* at ¶ [0144].

transgenes, *in vitro*.[29] For example, Girouard explicitly states that "donor cells are condition in vitro to introduce one or more desirable gene products (transgenes) to the cells."[30] At no time does Girouard disclose or suggest that donor cells may be subjected to transgenes that encodes connexin-42 or connexin-43 *in vivo*, as the Examiner asserts. With respect to the *in vivo* cell therapy techniques, Girouard merely states that donor cells can be delivered to a region of tissue to be treated. Girouard further discloses that in a different embodiment, there may be an additional step of preparing the donor cells before administering the cell therapy, such as by conditioning the donor cells *in vitro* to introduce one or more desirable gene products to the cells.[31] This clearly indicates that Girouard does not contemplate the delivery of a genetic material to a tissue site.

FIGS. 1A and 1C, which the Examiner relied on to assert that Girouard does not require an *in vitro* conditioning step, do not disclose that no *in vitro* conditioning step is required. FIG. 1A is a general flow diagram for providing combined cell and electrical therapy, and is not specific to examples in which donor cells that are subjected to transgenes. Girouard does not state that FIG. 1A is applicable to donor cells that have one or more desirable gene products, nor does Girouard state that the donor cells are conditioned with gene products *in vivo*, as apparently asserted by the Examiner. However, with respect to FIG. 1B, Girouard mentions that the "donor cells are conditioned *in vitro* to introduce one or more desirable gene products (transgenes) to the cells."[32]

Girouard discloses that FIG. 1C is a flow diagram showing a particular therapy for treating cardiac tissue suing combined cell and electrical therapies. With respect to FIG. 1C, Girouard states that "[o]nce the damaged tissue is located, the localized area may be treated by inserting or applying donor cells."[33] As with FIG. 1A, Girouard does not disclose that the donor cells are conditioned with gene products *in vivo* or that the donor cells referred to in FIG. 1C are even conditioned with gene products. To the extent Girouard discloses conditioning donor cells

[29] *Id.* at ¶ [0129].
[30] *Id.* at ¶ [0076].
[31] *Id.*
[32] *Id.* at ¶ [0076].
[33] *Id.* at ¶ [0081].

to introduce one or more desirable gene products to the cells, Girouard states that it is done *in vitro*.

The fact that a certain characteristic may be present in the prior art is not sufficient to establish the inherency of that result or characteristic.[34] The Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.[35] No reasonable support has been provided for the determination that FIGS. 1A and 1C of Girouard disclose that donor cells can be conditioned *in vivo* to introduce one or more desirable gene products (transgenes) to the cells.

For at least these reasons, Girouard does not support the Examiner's assertion that all genetic material disclosed by Girouard is configured to be applied *in vitro* and *in vivo*. The rejection of independent claim 21 should be reversed on the at least the ground that the Examiner has mischaracterized the Girouard disclosure to support the rejection of independent claim 21.

The Examiner stated that "Appellant has provided no evidence that [genetic material that causes the expression of connexin] isolated in vector form is somehow unusable *in vivo*, and Girouard discloses the contrary." Appellant, however, is not asserting that genetic material that causes the expression of connexin is unusable *in vivo*. Rather, in the Appeal Brief, Appellant noted that even if Soykan was modified in view of Heil, and further in view of Girouard, the resulting lead would not include each and every element of Appellant's claim 21 because, for example, the cited references fail to disclose or suggest the elution of a genetic material that causes expression of at least one of a connexin or a gap-junction by tissue at a stimulation site. As discussed above and in the Appeal Brief, Girouard does not disclose that genetic material that causes the expression of connexin is usable *in vivo*. As discussed in the Appeal Brief, contrary to the Examiner's assertions, neither Soykan nor Girouard provides any indication that expression of connexin, which takes place *ex vivo* in the Girouard reference, may be simply substituted in the *in vivo* technique disclosed by Soykan, as asserted by the Examiner.[36]

[34] *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993); MPEP § 2112.
[35] *Ex parte Levy*, 17 USPQ.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original); MPEP 2112.
[36] Final Office Action dated January 23, 2009 at p. 6, item 13 (Response to Arguments section).

For at least these reasons and the reasons discussed in the Appeal Brief filed on June 18, 2010, the Examiner has failed to establish a *prima facie* case for non-patentability of Appellant's independent claim 21 under 35 U.S.C. § 103(a). Claims 22–24, 26, and 29–33 depend from claim 21 and are patentable over Soykan in view of Heil and Girouard for at least the reasons discussed above with respect to independent claims 21.

CLAIM 46

Claim 46 specifies that the lead of independent claim 21 includes a chamber body defining a chamber that contains a polymeric matrix that absorbs a genetic material and elutes the genetic material to tissue at a stimulation site within a patient via a porous electrode, where the genetic material is adapted to cause expression of at least one of a connexin or a gap-junction by the tissue at the stimulation site to increase the conductivity of the tissue at the stimulation site and create a preferential conduction pathway between the stimulation site and at least one of a bundle of His or a Purkinje fiber of a heart of the patient. The cited art fails to disclose or suggest the lead of claim 46.

In support of the rejection of claim 46, the Examiner stated that claim 46 is directed to an inherent feature of Soykan and reasoned that "[b]ecause Soykan is in effect creating new contractile tissue around the stimulation device, this inherently creates a new arbitrary 'preferred conduction pathway.'"[37] As discussed in the Appeal Brief filed on June 18, 2010, the Examiner is relying on an improper finding of an inherent disclosure in Soykan to support the rejection of claim 46. The creation of "new contractile tissue" around a stimulation device does not in any way suggest that the "new contractile tissue" defines a pathway that is more conductive than another.

In the Examiner's Answer, the Examiner reiterated the assertion that because claim 46 "does not require the optimum, shortest (or even shorter) pathway, and does not indicate who or what 'prefers' the new conduction pathway," a path that is preferred by current or action potential to a pre-therapy path is a "preferential conduction pathway." As discussed in further

[37] Final Office Action dated January 23, 2009 at p. 7, item 15 (Response to Arguments section).

detail in the Appeal Brief, the Examiner's interpretation of the phrase "preferential conduction pathway" is unreasonable when Appellant's specification is properly considered. In view of Appellant's specification, it is clear that a preferential conduction pathway is a pathway that is preferred relative to other existing and available pathways for electrical conduction.

In the Examiner's Answer, the Examiner stated that "claim 46 is an apparatus claim with a functional recitation of the genetic material," and, therefore, the genetic material need only be capable of creating a preferred conduction pathway in order to disclose the genetic material of claim 46.[38] Claim 46, however, recites a specific medical lead that is not obvious in view of the cited art. Claim 46 requires a genetic material that causes expression of at least one of a connexin or a gap-junction by the tissue at the stimulation site to increase the conductivity of the tissue at the stimulation site in a way that creates a preferential conduction pathway to the bundle of His or a Purkinje fiber. Thus, the genetic material recited in claim 46 increases the conductivity of the tissue relative to other (e.g., adjacent) tissue through which the stimulation may also traverse.[39] Neither Soykan nor any of the other references disclose a genetic material that increases the conductivity of tissue relative to other (e.g., adjacent) tissue through which the stimulation may also traverse. For example, Soykan discloses the conversion of noncontractile cells to contractile cells, which does not necessarily increase conductivity of tissue relative to other tissue through which the stimulation may traverse.

For at least these reasons and the reasons discussed in the Appeal Brief filed on June 18, 2010, the Examiner has failed to establish a *prima facie* case for non-patentability of Appellant's claim 46 under 35 U.S.C. § 103(a), and the rejection of claim 46 should be reversed.

[38] Examiner's Answer dated September 1, 2010 at p. 12.
[39] *See* Appellant's disclosure at p. 6, ll. 8–12.

CONCLUSION

For at least these reasons and the reasons discussed in Appellant's Appeal Brief filed on June 18, 2010, the Examiner has failed to meet the burden of establishing a *prima facie* case of nonpatentability with respect to Appellant's claims 21–24, 26, 29–33, 35–42, and 46–54. In view of Appellant's arguments present in this Reply Brief and in the previously filed Appeal Brief, the rejection of Appellant's claims was improper and should be reversed. Reversal of all pending rejections and allowance of all pending claims is respectfully requested.

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